CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-571
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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Among two Phase III studies, one the them (16-002) showed enough evidence of drug efficacy in patients with suspected bacterial corneal ulcers for ITT and PP population. However the other study (16-003) is in the boundary, because it failed to show enough evidence of efficacy for Per Protocol population based on sensitivity analyses for discontinued patients. For modified Per Protocol population, which was defined by agency medical officer, both studies failed to show enough evidence of drug efficacy. Therefore, approval may depend on how important the analyses are.

1.2 Brief Overview of Clinical Studies

Two active-controlled, multicenter Phase II/III pivotal trials were conducted to support safety and efficacy. Study 16-002 was a North American study (US, Canada, Puerto Rico) in adults and children and Study 16-003 was an international study (India, Israel, Brazil) in adults suspected bacterial corneal ulcer only in one eye. These studies employed identical protocol designs except for the minimal age limit, which was 2 years in Study 16-002 and 18 years in Study 16-003. The active control in both Phase II/III studies was Ocuflox, and non-inferior test was used for comparison.

These studies were prospective, randomized, parallel-group, multicenter, double-masked, safety and efficacy trial in which 1.5% LVFX was compared with 0.3% OFLX in patients who had a clinical diagnosis of suspected bacterial corneal ulcer only in one eye. Patients instilled 1 to 2 drops of 1.5% LVFX or 0.3% OFLX in the study eye every 2 hours while awake, and approximately 4 and 6 hours after retiring, on Day 1 through 3 and then 4 times daily (approximately every 4 hours) while awake from Day 4 through completion – either attain clinical cure (see below) or finish the study schedule (18 days). The primary efficacy variable was clinical cure. A patient was considered clinically cured when the ulcer re-epithelialized and there was no progression from Baseline of the stromal infiltrate. After clinical cure was noted, patients were seen again in 2 to 5 days at a confirmatory visit. The cure rate difference between treatment group of –20% was used for non-inferior test margin. In addition to cure rate analysis, agency requested the sponsor to submit the analysis results of clinical cure with confirmation at Confirmatory Visit.

1.3 Statistical Issues and Findings

- The cure rate in the 1.5% LVFX treatment group showed non-inferior with margin of –20% compare to 0.3% OFLX treatment group for both studies and both ITT and PP populations. See the Table 3 and Table 10 of appendix.
- Sensitivity analyses were performed for discontinued patients. The results showed that PP population in study 16-003 did not support the non-inferior conclusion with margin of –20%,

in other words, the lower limit of CI was less than –20%. See the Table 12 and Table 13 of appendix.

- Analysis results of *cure rate with confirmation* preserved the non-inferiority results with *cure rate* for study 16-002 for both ITT and PP group. However, for study 16-003, the results showed non-inferior only for ITT group and failed to show non-inferiority with the lower limit of CI of –24.0% for PP group. See Table 6 and Table 14 of appendix.
- For modified PP population, analysis results of cure rate showed non-inferior for both studies. However, cure rate with confirmation failed to show non-inferior for both studies, the lower limit of CI was –20.7% for study 16-002 and –24.3% for study 16-003. See Table 7 and Table 15 of appendix.

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2 INTRODUCTION

2.1 Overview

Four clinical studies are submitted in this NDA to support the efficacy and safety of 1.5% LVFX for treatment of corneal ulcers, two Phase I trials and two Phase II/III pivotal studies. The two Phase I clinical pharmacology studies (16-001, 16-006) of 1.5% LVFX described in this submission were conducted in healthy volunteers with asymptomatic eyes to investigate the safety after topical ocular application. In addition, two active-controlled, multicenter Phase II/III pivotal trials were conducted to support safety and efficacy. Study 16-002 was a North American study (US, Canada, Puerto Rico) in adults and children and Study 16-003 was an international study in adults suspected bacterial corneal ulcer only in one eye. These studies employed identical protocol designs except for the minimal age limit, which was 2 years in Study 16-002 and 18 years in Study 16-003. The active control in both Phase II/III studies was Ocuflox, and non-inferior test was used for comparison. This review covered two Phase II/III studies (16-002, 16-003), but not Phase I studies.

2.2 Data Sources

Hard copy: Module 2 Vol 1, Module 5 Vol 1 through 22.

Electronic files: \\CDSESUB1\N21571\N_000

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3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study 16-002

3.1.1.1 Study Design and Endpoints

This was a prospective, randomized, parallel-group, multicenter, double-masked, safety and efficacy trial in which 1.5% LVFX was compared with 0.3% OFLX in patients 2 years of age or older who had a clinical diagnosis of suspected bacterial corneal ulcer only in one eye. At Baseline (Visit 1, Day 1), demographic information, medical, medication, and surgical histories, and pregnancy and contraceptive status (if female of childbearing potential) were recorded. Patients were assessed for ocular signs (biomicroscopy) and symptoms and best-corrected visual acuity (BCVA, by ETDRS chart), and had an undilated ophthalmoscopy, a bacteriologic corneal culture, and a pregnancy test (females). Medication was dispensed and dosing began on Day 1. Patients instilled 1 to 2 drops of 1.5% LVFX or 0.3% OFLX in the study eye every 2 hours while awake, and approximately 4 and 6 hours after retiring, on Day 1 through 3 and then 4 times daily (approximately every 4 hours) while awake from Day 4 through completion – either attain clinical cure (defined in the next section) or finish the study schedule (18 days). At Visit 2 (Day 2 or 3), patients updated their medical and medication histories, were questioned about adverse events (AEs) and compliance with the dosing regimen, and were evaluated for clinical signs (biomicroscopy) and symptoms, BCVA, and the investigator's clinical impression. Follow-up visits identical to Visit 2 were scheduled for Days 5 (± 1), 8 (± 1), 12 (± 2), and 18 (± 3). After clinical cure was noted, patients were seen again in 2 to 5 days at a confirmatory visit, and were evaluated by biomicroscopy, symptom assessment, the investigator's clinical impression, BCVA, ophthalmoscopy, and bacterial conjunctival culture. Investigators had the option of continuing treatment with study medication after clinical cure if they felt it was in the patient's best interest.

3.1.1.2 Efficacy measurements

- Epithelial defect size measured in square millimeters (mm^2) and graded as absent, mild ($<4mm^2$), moderate (4 to $<8mm^2$), or severe ($.8mm^2$).
- Focal stromal infiltrate area measured in mm^2 and graded as absent ($<0.5mm^2$), mild (0.5 to $<3mm^2$), moderate (3 to $<8mm^2$), or severe ($.8mm^2$).
- Depth of stromal infiltrate measured on a 4-point scale as absent (0), superficial (1), middle (2), and deep (3).
- Investigator's clinical impression (cured, improved, no change, or worse) was recorded at all visits except Baseline.

The primary efficacy variable was clinical cure. A patient was considered clinically cured when the ulcer re-epithelialized and there was no progression from Baseline of the stromal infiltrate. The size of the epithelial defect was rounded to the nearest 0.1 mm^2. Values less than 0.05 mm

were rounded to 0.0 and considered re-epithelialized. Progression of the stromal infiltrate was based on the area of the infiltrate in mm^2. No progression of the stromal infiltrate was defined as an infiltrate area that was the same or less than at the baseline examination.

3.1.1.3 Patient Disposition and Demographic

Enrollment totaled 237 patients (164 culture positive) treated by 29 investigators at 28 sites: 121 patients received 1.5% LVFX and 116 received 0.3% OFLX. A total of 203 (86%) patients completed the study: 108 (89%) in the 1.5% LVFX group and 95 (82%) in the 0.3% OFLX group. ITT analyses included 237 patients (121 and 116, respectively), and the PP analysis included 149/237 patients (63%): 78 and 71, respectively. Eighty-eight patients were excluded from the PP population for the following reasons: negative baseline bacterial culture (71), significant protocol deviations (12), absence of post-baseline data (3), medical monitor decision (1), or concomitant fungal infection (1).

Demographics are summarized by treatment groups in Table 2 of appendix. As shown, patients are balanced.

3.1.1.4 Statistical Methodologies

Efficacy analysis populations are defined as follow:

> ITT: The population included all enrolled patients in the study who received at least one dose of study medication and had efficacy data measured after their first dose.
>
> PP: The PP population included all patients in the ITT population who also had a positive corneal bacterial culture from the study eye; did not have a fungal, viral, or parasitic infection in the study eye; and did not have any significant protocol deviations (e.g., concomitant administration of non-study antimicrobial medication). All the protocol deviations significant enough to warrant exclusion of all or part of a patient's data from the PP analysis were defined and documented before unmasking the study.

The hypothesis of interest was that the cure rate at Endpoint in the 1.5% LVFX group would be equivalent to or better than that in the 0.3% OFLX group. (Endpoint is the visit at which clinical cure was first noted or, for patients not cured, the last examination while receiving the treatment for both ITT and PP group). Equivalence or better was defined as a difference between the cure rate at Endpoint for 1.5% LVFX and for 0.3% OFLX of not less than -20%. This was to be demonstrated by computing the lower limit of a one-sided 97.5% confidence interval (CI) on the difference between treatments in cure rates using the normal approximation. Because of the small sample size at each study site, the 97.5% CI was not weighted by size of study site.

The difference between treatment groups in cure rate was analyzed using the CMH statistic stratified by study site. Some sites enrolled very few patients who were culture positive at baseline. At sites with only one or two such patients, all the data could come from only one treatment. In the CMH analyses stratified by study site, data from those sites evaluating only one

treatment would not contribute to estimates of overall differences between treatments. To avoid this loss of data, data from such sites were pooled into a single block.

After the study was unmasked, the Breslow-Day test was added to the analysis of clinical cure rate to determine whether the difference between treatments was consistent across investigative sites (referred to as a test of homogeneity). This statistic was calculated for both the PP and the ITT patient populations.

Reviewer's Comments

- Sponsor planned two different analysis methods in their protocol, one of the method is to compare the difference between treatments in cure rates using the normal approximation, and the other method is to compare the difference between treatment groups analyzed using the CMH statistic stratified by study site. However, in the final report, sponsor submitted only one results of primary efficacy analysis. The final report specified the result is using CMH method, however, sponsor's analysis results can be reproduced by analyzing mean difference using the normal approximation without any adjustment of center effects. In fact, CMH method is based on the risk ratio of two treatment groups, but not the difference. It is not even possible to analyze using CMH in this case, because the non-inferiority margin (-20%) was based on the difference, but not on the ratio.
- After clinical cure was noted, patients were seen again in 2 to 5 days at a confirmatory visit, and were evaluated by many categories (See the last part of "3.1.1.1 Study design and Endpoints" above). Agency requested the sponsor to submit the analysis results of clinical cure with confirmation at Confirmatory Visit.
- In addition to two population (ITT and PP), modified PP was defined by medical officer, which is the subset of sponsor's PP. The efficacy analyses were performed for this population by this reviewer.

3.1.1.5 Results and Conclusions

In the ITT population, the 1.5% LVFX group cure rate was 90.1% (109/121) and the 0.3% OFLX group cure rate was 87.9% (102/116). The difference in cure rates was 2.2%, and the lower limit of the one-sided 97.5% CI of this difference, –5.8%, did not exceed –20% (demonstrating equivalent cure rates). Some discontinued patients were cured (See reviewer's comments below). In the PP population, the cure rate was 94.9% (74/78) in the 1.5% LVFX group and 95.8% (68/71) in the 0.3% OFLX group. The difference in cure rates between the treatment groups was –0.9%, and the lower limit of the one-sided 97.5% CI of this difference, –7.7%, did not exceed the maximal allowable difference of –20%, demonstrating that 1.5% LVFX and 0.3% OFLX had equivalent clinical cure rates.

Reviewer's comments

- In addition to sponsor's analysis, this reviewer calculated the confidence interval of the difference between treatments in cure rates using the normal approximation adding study

center indications as factor. Small centers were pooled as sponsor suggested. They showed the similar results with sponsor's, and summarized in the Table 4 of appendix.

- As shown above, only 86% of the subjects completed, and others discontinued. Among 13 subjects discontinued from 1.5% LVFX treated group, 3 (23%) subjects were cured. A sensitivity analysis was performed by reviewer using following imputation: For 1.5% LVFX group, impute as not cured for all the discontinued subject, and for 0.3% OFLX group, use as defined. Therefore, only three subjects will be changed in this sensitivity analysis. The results support the sponsor's results and are summarized in the Table 5 of appendix.
- Analysis results of cured rate with confirmation are summarized in the Table 6 of appendix. As shown, statistical comparison results are consistent.
- For modified PP group, both cured rate and cured rate with confirmation were compared between two groups and summarized at Table 7. The cured rate with confirmation in modified PP failed to show non-inferiority because the lower limit of the confidence interval was –20.7% which exceeded –20%.

3.1.2 Study 16-003

3.1.2.1 Study Design and Endpoints

Study 16-003 was an international study (India, Israel, and Brazil) while study 16-002 was a North American study (US, Canada, Puerto Rico). These studies employed identical protocol designs except for the minimal age limit, which was 2 years in Study 16-002 and 18 years in Study 16-003.

3.1.2.2 Efficacy measurements

Identical to the Study 16-002.

3.1.2.3 Patient Disposition and Demographic

In total, 199 patients were enrolled, of whom 76% (151/199) completed the study, including 76% (74/98) in the 1.5% LVFX group and 76% (77/101) in the 0.3% OFLX group. Forty-eight patients (24%, 48/199) were discontinued from the study (24 patients in each treatment group); the overall rate for discontinuation was similar between treatment groups. The most frequent reason for discontinuation was treatment failure. Discontinuations because of treatment failure were half as frequent in the 1.5% LVFX group (29%, 7/24) compared with the 0.3% OFLX group (58%, 14/24). Two patients never returned after their baseline visit and are considered lost to follow-up.

Demographics are summarized by treatment groups in Table 9 of appendix. As shown, patients are balanced.

3.1.2.4 Statistical Methodologies

Identical to the Study 16-002. Therefore, same reviewer's comments can be applied.

3.1.2.5 Results and Conclusions

In the ITT population, the 1.5% LVFX group cure rate was 83.7% (82/98) and the 0.3% OFLX group cure rate was 82.2% (83/101). The difference in cure rates was 1.5%, and the lower limit of the one-sided 97.5% CI of this difference, -8.9%, did not exceed –20% (demonstrating equivalent cure rates). In the PP population, the cure rate at Endpoint was 79.9% (55/69) in the 1.5% LVFX group and 85.5% (53/62) in the 0.3% OFLX group. The difference in cure rates between the treatment groups was –5.8%, and the lower limit of the one-sided 97.5% CI of this difference, -18.7%, very close but did not exceed the maximal allowable difference of –20%, demonstrating the 1.5% LVFX and 0.3% OFLX had equivalent clinical cure rates.

Reviewer's comments

- Similar to study 16-002, same additional analyses were performed. They showed the similar results with sponsor's, and the results are summarized in the Table 11 of appendix.
- Same sensitivity analysis to the study 16-002 was performed. Among 24 discontinued subjects in 1.5% LVFX group, 8 (33%) of them were cured. For ITT, the non-inferiority result was preserved. However, for PP, the lower limit of CI of difference between treatment groups in cure rate exceeds –20% with –26.7%. The results are summarized in the Table 12 of appendix.
- Note that PP population includes who had a positive corneal bacterial culture, while ITT includes suspected positive corneal bacterial culture.
- Additional sensitivity analysis was performed by imputing as not cured for discontinued patients for both treatment groups. Among 24 discontinued patients in 0.3% OFLX group, 6 (25%) of them were cured. However, this method also exceeded –20% with -24.0%. See Table 13 of appendix. Note that this method is less conservative than the original sensitivity analysis. Accordingly, based on the sensitivity analyses, study 16-003 failed to show the non-inferiority for PP group.
- For analyses of cure rate with confirmation, ITT group preserved the non-inferiority result, but PP group failed to show non-inferiority with lower limit of CI of –24.0%. Details are summarized in the Table 14 of appendix.
- For modified PP group, both cured rate and cured rate with confirmation were compared between two groups and summarized at Table 15. As shown, the cured rate with confirmation

in modified PP also failed to show non-inferiority because the lower limit of the confidence interval was –24.3% which exceeded –20%.

3.2 Evaluation of Safety

Safety data were not reviewed.

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Additional analyses including gender, age, treatment group, and interaction between treatment groups and demographic variables as factors were performed by this reviewer for primary efficacy variables for each study. None of the interactions between treatment and demographic variables showed significant results. No further issues were found.

4.2 Other Special/Subgroup Populations

No further subgroup analyses were performed.

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5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- The cure rate in the 1.5% LVFX treatment group showed non-inferior with margin of –20% compare to 0.3% OFLX treatment group for both studies and both ITT and PP populations. See the Table 3 and Table 10 of appendix.
- Sensitivity analyses were performed for discontinued patients. The results showed that PP population in study 16-003 did not support the non-inferior conclusion with margin of –20%, in other words, the lower limit of CI was less than –20%. See the Table 12 and Table 13 of appendix.
- Analysis results of *cure rate with confirmation* preserved the non-inferiority results with *cure rate* for study 16-002 for both ITT and PP group. However, for study 16-003, the results showed non-inferior only for ITT group and failed to show non-inferiority with the lower limit of CI of –24.0% for PP group. See Table 6 and Table 14 of appendix.
- For modified PP population, analysis results of cure rate showed non-inferior for both studies. However, cure rate with confirmation failed to show non-inferior for both studies, the lower limit of CI was –20.7% for study 16-002 and –24.3% for study 16-003. See Table 7 and Table 15 of appendix.

5.2 Conclusions and Recommendations

Among two Phase III studies, one the them (16-002) showed enough evidence of drug efficacy in patients with suspected bacterial corneal ulcers for ITT and PP population. However the other study (16-003) is in the boundary, because it failed to show enough evidence of efficacy for Per Protocol population based on sensitivity analyses for discontinued patients. For modified Per Protocol population, which was defined by agency medical officer, both studies failed to show enough evidence of drug efficacy. Therefore, approval may depend on how important the analyses are.

6 APPENDICES

Table 1. Summary of Patient Disposition; Study 16-002

	1.5% LVFX	0.3% OFLX	Total
Number of patients enrolled	121	116	237
Number of patients completed	108 (89.3%)	95 (81.9%)	203 (85.7%)
Number of patients discontinued	13 (10.7%)	21 (18.1%)	34 (14.3%)
Reasons for Discontinuation			
Treatment failure	3 (23.1%)	7 (33.3%)	10 (29.4%)
Lost to follow-up	4 (30.8%)	6 (28.6%)	10 (29.4%)
Noncompliance	0 (0%)	4 (19.0%)	4 (11.8%)
Adverse event (AE)	1 (7.7%)	1 (4.8%)	2 (5.9%)
Patient decision not associated with AE	1 (7.7%)	1 (4.8%)	2 (5.9%)
Other	4 (30.8%)	2 (9.5%)	6 (17.6%)

Table 2. Summary of Demographic; Study 16-002

	ITT		PP	
	1.5% LVFX	0.3% OFLX	1.5% LVFX	0.3% OFLX
Number of patients	121	116	78	71
Age – Mean (SD)	42.9 (19.2)	38.9 (16.9)	40.4 (17.4)	39.4 (15.4)
Gender				
Male	59 (48.8%)	58 (50.0%)	42 (53.8%)	41 (57.7%)
Female	62 (51.2%)	58 (50.0%)	36 (46.2%)	30 (42.3%)
Race				
Caucasian	78 (64.5%)	72 (62.1%)	48 (61.5%)	44 (62.0%)
Black	13 (10.7%)	16 (13.8%)	9 (11.5%)	12 (16.9%)
Asian	9 (7.4%)	6 (5.2%)	5 (6.4%)	3 (4.2%)
Hispanic	18 (14.9%)	15 (12.9%)	13 (16.7%)	7 (9.9%)
Asian Indian	2 (1.7%)	4 (3.4%)	2 (2.6%)	3 (4.2%)
Other	1 (0.8%)	2 (1.7%)	1 (1.3%)	1 (1.4%)
Not recorded	0 (0%)	1 (0.9%)	0 (0%)	1 (1.4%)

Table 3. Summary of Clinical Cure at Endpoint; Study 16-002

Population	Treatment		Treatment Comparison [a]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	109/121 (90.1%)	102/116 (87.9%)	2.2%	-5.8%	0.53
PP	74/78 (94.9%)	68/71 (95.8%)	-0.9%	-7.7%	0.88

a. 95% CI (97.5% for one-side) of difference in cure rate using normal approximation

Table 4. Summary of Clinical Cure at Endpoint with center effect; Study 16-002

Population	Treatment		Treatment Comparison [a]		
	1.5% LVFX N(%)[b]	0.3% OFLX N(%)[b]	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	109/121 (92.2%)	102/116 (89.5%)	2.6%	-5.4%	0.52
PP	74/78 (94.9%)	68/71 (95.8%)	-0.6%	-7.6%	0.87

a. 95% CI (97.5% for one-side) of difference in cure rate using 2-way ANOVA with factor of treatment group and center indications. Small centers were pooled as sponsor suggested.

Table 5. Summary of Sensitivity Analysis for Clinical Cure at Endpoint; Study 16-002

Population	Treatment [a]		Treatment Comparison [b]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	106/121 (87.6%)	102/116 (87.9%)	-0.3%	-8.7%	0.94
PP	71/78 (91.0%)	68/71 (95.8%)	-4.7%	-12.6%	0.24

a. Discontinued patients are considered as not cured for 1.5% LVFX treated patients.
b. 95% CI (97.5% for one-side) of difference in cure rate using normal approximation

Table 6. Summary of Confirmed to Clinical Cure with confirmation; Study 16-002

Population	Treatment		Treatment Comparison [a]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	99/121 (81.8%)	88/116 (75.9%)	6.0%	-4.4%	0.26
PP	68/78 (87.2%)	61/71 (85.9%)	1.3%	-9.7%	0.88

a. 95% CI (97.5% for one-side) of difference in cure rate with confirmation using normal approximation

Table 7. Summary of Clinical Cure at Endpoint and Clinical Cure with confirmation for modified PP population; Study 16-002

Efficacy Variable	Treatment		Treatment Comparison [a]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
Clinical Cure at Endpoint	38/41 (92.7%)	29/31 (93.5%)	-0.8%	-12.6%	0.89
Clinical Cure with Confirmation	34/41 (82.9%)	27/31 (87.1%)	-4.2%	-20.7%	0.62

a. 95% CI (97.5% for one-side) of difference in cure rate using normal approximation

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Table 8. Summary of Patient Disposition; Study 16-003

	1.5% LVFX	0.3% OFLX	Total
Number of patients enrolled	98	101	199
Number of patients completed	74 (75.5%)	77 (76.2%)	151 (75.9%)
Number of patients discontinued	24 (24.5%)	24 (23.8%)	48 (24.1%)
Reasons for Discontinuation			
Treatment failure	7 (29.2%)	14 (58.3%)	21 (43.8%)
Lost to follow-up	11 (45.8%)	4 (16.7%)	15 (31.3%)
Patient decision not associated with AE	3 (12.5%)	3 (12.5%)	6 (12.5%)
Adverse event (AE)	2 (8.3%)	0 (0%)	2 (4.2%)
Noncompliance	1 (4.2%)	0 (0%)	1 (2.1%)
Other	0 (0%)	3 (12.5%)	3 (6.3%)

Table 9. Summary of Demographic; Study 16-003

	ITT		PP	
	1.5% LVFX	0.3% OFLX	1.5% LVFX	0.3% OFLX
Number of patients	98	101	69	62
Age – Mean (SD)	43.7 (14.7)	43.9 (16.3)	43.9 (14.4)	45.6 (16.5)
Gender				
Male	67 (68.4%)	61 (60.4%)	47 (68.1%)	38 (58.1%)
Female	31 (31.6%)	40 (39.6%)	22 (31.9%)	26 (41.9%)
Race				
Caucasian	29 (29.6%)	27 (26.7%)	12 (17.4%)	14 (22.6%)
Black	0 (0%)	1 (1.0%)	0 (0%)	1 (1.6%)
Hispanic	2 (2.0%)	3 (3.0%)	2 (2.9%)	3 (4.8%)
Asian Indian	67 (68.4%)	70 (69.3%)	55 (79.7%)	44 (71.0%)

Table 10. Summary of Clinical Cure at Endpoint; Study 16-003

Population	Treatment		Treatment Comparison [a]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	82/98 (83.7%)	83/101 (82.2%)	1.5%	-8.9%	0.76
PP	55/69 (79.7%)	53/62 (85.5%)	-5.8%	-18.7%	0.67

a. 95% CI (97.5% for one-side) of difference in cure rate using normal approximation

Table 11. Summary of Clinical Cure at Endpoint with center effect; Study 16-003

Population	Treatment		Treatment Comparison [a]		
	1.5% LVFX N(%)[b]	0.3% OFLX N(%)[b]	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	82/98 (90.4%)	83/101 (88.9%)	1.5%	-8.7%	0.77
PP	55/69 (88.5%)	53/62 (91.2%)	-2.8%	-15.6%	0.67

a. 95% CI (97.5% for one-side) of difference in cure rate using 2-way ANOVA with factor of treatment group and center indications. Small centers were pooled as sponsor suggested.

Table 12. Summary of Sensitivity Analysis for Clinical Cure at Endpoint; Study 16-003

Population	Treatment [a]		Treatment Comparison [b]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	74/98 (75.5%)	83/101 (82.2%)	-6.7%	-18.0%	0.25
PP	50/69 (72.5%)	53/62 (85.48%)	-13.0%	-26.7%	0.06

a. Discontinued patients are considered as not cured for 1.5% LVFX treated patients.
b. 95% CI (97.5% for one-side) of difference in cure rate using normal approximation

Table 13. Summary of Other Sensitivity Analysis for Clinical Cure at Endpoint; Study 16-003

Population	Treatment [a]		Treatment Comparison [b]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	74/98 (75.5%)	77/101 (76.2%)	-0.7%	-12.6%	0.90
PP	50/69 (72.5%)	51/62 (82.3%)	-9.8%	-24.0%	0.18

a. Discontinued patients are considered as not cured for both treatment group.
b. 95% CI (97.5% for one-side) of difference in cure rate using normal approximation

Table 14. Summary of Clinical Cure with confirmation; Study 16-003

Population	Treatment		Treatment Comparison [a]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
ITT	74/98 (75.5%)	77/101 (76.2%)	-0.7%	-12.6%	0.90
PP	50/69 (72.5%)	51/62 (82.3%)	-9.7%	-24.0%	0.17

a. 95% CI (97.5% for one-side) of difference in cure rate with confirmation using normal approximation

Table 15. Summary of Clinical Cure at Endpoint and Clinical Cure with confirmation for modified PP population; Study 16-003

Efficacy Variable	Treatment		Treatment Comparison [a]		
	1.5% LVFX N(%)	0.3% OFLX N(%)	Difference (%)	Lower 97.5% CI Limit	P-value
Clinical Cure	45/58 (77.6%)	43/52 (82.7%)	-5.1%	-19.97%	0.50
Clinical Cure with Confirmation	41/58 (70.7%)	41/52 (78.8%)	-8.2%	-24.3%	0.32

a. 95% CI (97.5% for one-side) of difference in cure rate using normal approximation

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